81640 9B07 LB

LB

Access DB# _____

SEARCH REQUEST FORM

RECEIVED
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Scientific and Technical Information Center

(STIC)

Requester's Full Name: Jeffrey E. Russel Examiner #: 62785 Date: 12.4.2002

Art Unit: 1654 Phone Number 308-3975 Serial Number: 09/758,793

Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

CM1-9D13/CM1-9807

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Tetrapartate Prodrugs

Inventors (please provide full names): R. Greenwald, H. Zhao

Earliest Priority Filing Date: 1-12-2001

Contact:
~~Toby~~ Port
~~Technical Info. Specialist~~
CM1 9A04
~~TC: 3089~~
308-3534

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search SEQ ID NO:1 (GFLG) in STN, in the U.S. patet application sequace database, and in Geneseq/Swissprot/PIR. Please require any hits to have 8 or fewer residues.

Thank you.
JER

AA 12.4

****

STAFF USE ONLY

Searcher: _____

Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: 12/5

Date Completed: 12/6

Searcher Prep & Review Time: 12 | 15

Clerical Prep Time: _____

Online Time: 12 | 30

Type of Search

NA Sequence (#) _____

AA Sequence (#) _____

Structure (#) _____

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN 141

Dialog _____

Questel/Orbit _____

Dr.Link _____

Lexis/Nexis _____

Sequence Systems _____

WWW/Internet _____

Other (specify) _____

PTO-1590 (8-01)

8/2/03

GenCore version 5.1.3

OM protein - protein search, using sw model

Run on: December 6, 2002, 10:14:06 ; Search time 15 Seconds
(without alignments)
7.846 Million cell updates/sec

Title: US-09-758-993A-1
Perfect score: 22
Sequence: 1 GFLG 4

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 262574 seqs, 29422922 residues

Total number of hits satisfying chosen parameters: 262574

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1000 summaries

Database : Issued_Patents_AA:*
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4: /cgn2_6/ptodata/1/iaa/6B_COMB.pep:*
5: /cgn2_6/ptodata/1/iaa/PCTUS_COMB.pep:*
6: /cgn2_6/ptodata/1/iaa/backfiles1.pep:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description

1	22	100.0	4	1	US-07-822-924-1	Sequence 1, Appli
2	22	100.0	4	1	US-07-842-171-1	Sequence 1, Appli
3	22	100.0	4	1	US-08-064-892-1	Sequence 1, Appli
4	22	100.0	4	1	US-07-991-199D-2	Sequence 2, Appli
5	22	100.0	4	2	US-09-060-455-10	Sequence 10, Appl
6	22	100.0	4	4	US-09-183-557-1	Sequence 1, Appli
7	22	100.0	4	4	US-08-062-366-1	Sequence 1, Appli
8	22	100.0	4	4	US-09-128-572-21	Sequence 21, Appl
9	22	100.0	4	4	US-09-306-568A-1	Sequence 1, Appli
10	22	100.0	4	5	PCT-US93-00683-1	Sequence 1, Appli
11	22	100.0	4	5	PCT-US93-12246-2	Sequence 2, Appli
12	22	100.0	5	1	US-07-822-924-8	Sequence 8, Appli
13	22	100.0	5	1	US-07-969-307A-8	Sequence 8, Appli
14	22	100.0	5	2	US-09-060-455-17	Sequence 17, Appl
15	22	100.0	5	5	PCT-US93-00683-8	Sequence 8, Appli
16	22	100.0	6	1	US-07-822-924-9	Sequence 9, Appli
17	22	100.0	6	1	US-07-969-307A-11	Sequence 11, Appl
18	22	100.0	6	1	US-08-256-236-3	Sequence 3, Appli
19	22	100.0	6	1	US-08-256-236-6	Sequence 6, Appli
20	22	100.0	6	1	US-07-991-199D-7	Sequence 7, Appli
21	22	100.0	6	2	US-09-060-455-18	Sequence 18, Appl
22	22	100.0	6	5	PCT-US93-00228-3	Sequence 3, Appli
23	22	100.0	6	5	PCT-US93-00228-6	Sequence 6, Appli
24	22	100.0	6	5	PCT-US93-00683-9	Sequence 9, Appli
25	22	100.0	6	5	PCT-US93-12246-7	Sequence 7, Appli
26	22	100.0	7	1	US-07-969-307A-14	Sequence 14, Appl
27	22	100.0	8	1	US-07-969-307A-17	Sequence 17, Appl
28	22	100.0	8	2	US-08-249-830-11	Sequence 11, Appl
29	22	100.0	8	3	US-09-198-209-11	Sequence 11, Appl

ALIGNMENTS

RESULT 1
US-07-822-924-1
; Sequence 1, Application US/07822924
; Patent No. 5258453
; GENERAL INFORMATION:
; APPLICANT: J. Kopecek et al.
; TITLE OF INVENTION: A DRUG DELIVERY SYSTEM FOR THE
; TITLE OF INVENTION: SIMULTANEOUS DELIVERY OF DRUGS ACTIVATABLE BY ENZYMES AND
; TITLE OF INVENTION: LIGHT
; NUMBER OF SEQUENCES: Ten
; CORRESPONDENCE ADDRESS:

; ADDRESSEE: Thorpe, No. 5258453th & Western
; STREET: 9035 South 700 East, Suite 200
; CITY: Sandy
; STATE: Utah
; COUNTRY: USA
; ZIP: 84070
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Diskette, 3.5 inch, 720 Kb storage
; COMPUTER: compaq LTE/286
; OPERATING SYSTEM: DOS 4.01
; SOFTWARE: Word Perfect 5.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/07/822,924
; FILING DATE: 19920121
; CLASSIFICATION: 514
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: none
; FILING DATE: na
; ATTORNEY/AGENT INFORMATION:
; NAME: Western, M. Wayne
; REGISTRATION NUMBER: 22,788
; REFERENCE/DOCKET NUMBER: T377
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (801) 566-6633
; TELEFAX: (801) 566-0750
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 4
; TYPE: AMINO ACID
; TOPOLOGY: linear
US-07-822-924-1

Query Match 100.0%; Score 22; DB 1; Length 4;
Best Local Similarity 100.0%; Pred. No. 2e+05;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 1 GFLG 4

RESULT 2
US-07-842-171-1
; Sequence 1, Application US/07842171
; Patent No. 5387578

; GENERAL INFORMATION:
; APPLICANT: ANGELUCCI, Francesco
; APPLICANT: BERSANI, Laura
; APPLICANT: CARUSO, Michele
; APPLICANT: RIPAMONTI, Marina
; APPLICANT: RUGGIERI, Daniela
; APPLICANT: SUARATO, Antonino
; TITLE OF INVENTION: New Linker for Bioactive Agents
; NUMBER OF SEQUENCES: 1
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Oblon, Spivak, McClelland, Maier
; ADDRESSEE: & Neustadt PC
; STREET: Fourth Floor, 1755 Jefferson Davis
; STREET: Highway
; CITY: Arlington
; STATE: Virginia
; COUNTRY: USA
; ZIP: 22202
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/07/842,171
; FILING DATE: April 3rd, 1992
; CLASSIFICATION: 424
; ATTORNEY/AGENT INFORMATION:
; NAME: OBLON, No. 5387578man F
; REGISTRATION NUMBER: 24,618
; REFERENCE/DOCKET NUMBER: 769-267-0 PCT
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (703) 413-3000
; TELEFAX: (703)413-2220
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 4 amino acids
; TYPE: amino acid
; STRANDEDNESS: single
; TOPOLOGY: linear
; MOLECULE TYPE: peptide
US-07-842-171-1

Query Match 100.0%; Score 22; DB 1; Length 4;
Best Local Similarity 100.0%; Pred. No. 2e+05;

Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 1 GFLG 4

RESULT 6
US-09-183-557-1
; Sequence 1, Application US/09183557
; Patent No. 6180095
; GENERAL INFORMATION:
; APPLICANT: Greenwald, Richard B.
; APPLICANT: Pendri, Annapurna
; APPLICANT: Choe, Yun H.
; TITLE OF INVENTION: Polymeric Prodrugs of Amino- and Hydroxyl-Containing
; TITLE OF INVENTION: Bioactive Agents
; FILE REFERENCE: 1079cip
; CURRENT APPLICATION NUMBER: US/09/183,557
; CURRENT FILING DATE: 1998-10-30
; EARLIER APPLICATION NUMBER: 08/992,435
; EARLIER FILING DATE: 1997-12-17
; NUMBER OF SEQ ID NOS: 1
; SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 1
; LENGTH: 4
; TYPE: PRT
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Description of Artificial Sequence:Peptide
; OTHER INFORMATION: linker.
US-09-183-557-1

Query Match 100.0%; Score 22; DB 4; Length 4;
Best Local Similarity 100.0%; Pred. No. 2e+05;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 1 GFLG 4

RESULT 7
US-08-062-366-1

; Sequence 1, Application US/08062366
; Patent No. 6214345
; GENERAL INFORMATION:
; APPLICANT: Firestone, Raymond A.
; APPLICANT: Dubowchik, Gene M.
; TITLE OF INVENTION: LYSOSOMAL ENZYME-CLEAVABLE ANTITUMOR
; TITLE OF INVENTION: DRUG CONJUGATES
; NUMBER OF SEQUENCES: 2
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Bristol-Myers Squibb Company
; STREET: 3005 First Avenue
; CITY: Seattle
; STATE: Washington
; COUNTRY: USA
; ZIP: 98121
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.25
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/062,366
; FILING DATE: 14-MAY-1993
; CLASSIFICATION: 424
; ATTORNEY/AGENT INFORMATION:
; NAME: Bogden, James M.
; REGISTRATION NUMBER: 32,962
; REFERENCE/DOCKET NUMBER: CT2214-
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 206 727-3688
; TELEFAX: 206 727-3601
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 4 amino acids
; TYPE: amino acid
; TOPOLOGY: linear
; MOLECULE TYPE: peptide
US-08-062-366-1

Query Match 100.0%; Score 22; DB 4; Length 4;
Best Local Similarity 100.0%; Pred. No. 2e+05;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||

Db 1 GFLG 4

Search completed: December 6, 2002, 10:17:14
Job time : 30 secs

GenCore version 5.1.3

OM protein - protein search, using sw model

Run on: December 6, 2002, 10:17:06 ; Search time 10 Seconds
(without alignments)
6.497 Million cell updates/sec

Title: US-09-758-993A-1
Perfect score: 22
Sequence: 1 GFLG 4

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 103943 seqs, 16242309 residues

Total number of hits satisfying chosen parameters: 103943

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1000 summaries

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12: /cgn2_6/ptodata/1/pubpaa/US10_PUBCOMB.pep:*
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14: /cgn2_6/ptodata/1/pubpaa/US60_PUBCOMB.pep:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	22	100.0	9	10	US-09-834-765-516	Sequence 516, App
2	22	100.0	9	10	US-09-834-765-626	Sequence 626, App
3	22	100.0	9	10	US-09-954-349-6	Sequence 6, Appli
4	22	100.0	10	10	US-09-962-055-22	Sequence 22, Appl
5	22	100.0	10	10	US-09-834-765-399	Sequence 399, App
6	22	100.0	10	10	US-09-834-765-472	Sequence 472, App
7	22	100.0	10	12	US-10-023-529-22	Sequence 22, Appl
8	22	100.0	10	12	US-10-023-523-22	Sequence 22, Appl
9	22	100.0	11	10	US-09-966-871-37	Sequence 37, Appl
10	22	100.0	11	12	US-10-039-645-37	Sequence 37, Appl
11	22	100.0	16	9	US-10-044-034-6	Sequence 6, Appli
12	22	100.0	17	8	US-08-424-550B-305	Sequence 305, App
13	22	100.0	17	9	US-10-010-114-5	Sequence 5, Appli
14	22	100.0	19	10	US-09-954-349-2	Sequence 2, Appli
15	22	100.0	19	10	US-09-954-349-5	Sequence 5, Appli
16	22	100.0	23	9	US-10-010-114-4	Sequence 4, Appli
17	22	100.0	23	9	US-10-010-114-8	Sequence 8, Appli
18	22	100.0	25	10	US-09-911-838-215	Sequence 215, App
19	22	100.0	30	9	US-09-922-364A-33	Sequence 33, Appl
20	22	100.0	30	9	US-09-254-590-33	Sequence 33, Appl
21	22	100.0	32	9	US-10-010-114-2	Sequence 2, Appli
22	22	100.0	32	10	US-09-764-877-1256	Sequence 1256, Ap
23	22	100.0	35	9	US-09-798-128-15	Sequence 15, Appl
24	22	100.0	35	10	US-09-358-082A-20	Sequence 20, Appl
25	22	100.0	39	10	US-09-864-761-46859	Sequence 46859, A
26	22	100.0	42	10	US-09-814-122-34	Sequence 34, Appl
27	22	100.0	45	9	US-09-984-245-185	Sequence 185, App
28	22	100.0	45	10	US-09-864-761-36530	Sequence 36530, A
29	22	100.0	45	10	US-09-925-300-946	Sequence 946, App
30	22	100.0	46	10	US-09-925-302-818	Sequence 818, App

ALIGNMENTS

RESULT 1
US-09-834-765-516
; Sequence 516, Application US/09834765
; Patent No. US20020055478A1
; GENERAL INFORMATION:
; APPLICANT: Mary Faris
; APPLICANT: Pia M. Challita-Eid
; APPLICANT: Arthur B. Raitano
; APPLICANT: Steve Chappell Mitchell
; APPLICANT: Daniel E.H. Afar
; APPLICANT: Aya Jakobovits
; TITLE OF INVENTION: GTP-BINDING PROTEIN USEFUL IN TREATMENT
; TITLE OF INVENTION: AND DETECTION OF CANCER
; FILE REFERENCE: 129.6USU1
; CURRENT APPLICATION NUMBER: US/09/834,765
; CURRENT FILING DATE: 2001-09-21
; PRIOR APPLICATION NUMBER: 60/197,647
; PRIOR FILING DATE: 2000-04-12
; NUMBER OF SEQ ID NOS: 770
; SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 516
; LENGTH: 9
; TYPE: PRT
; ORGANISM: Homo sapiens
US-09-834-765-516

Query Match 100.0%; Score 22; DB 10; Length 9;
Best Local Similarity 100.0%; Pred. No. 8.6e+04;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
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Db 4 GFLG 7

Search completed: December 6, 2002, 10:25:08
Job time : 11 secs

GenCore version 5.1.3

OM protein - protein search, using sw model

Run on: December 6, 2002, 10:14:02 ; Search time 92 Seconds
(without alignments)
5.794 Million cell updates/sec

Title: US-09-758-993A-1
Perfect score: 22
Sequence: 1 GFLG 4

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 908470 seqs, 133250620 residues

Total number of hits satisfying chosen parameters: 908470

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1000 summaries

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3: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA1982.DAT:*
4: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA1983.DAT:*
5: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA1984.DAT:*
6: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA1985.DAT:*
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9: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA1988.DAT:*
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22: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA2001.DAT:*
23: /SIDS2/gcgdata/geneseq/geneseqp-embl/AA2002.DAT:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	22	100.0	4	13	AAR26364	Cyclosporin-polyme
2	22	100.0	4	15	AAR44693	Peptide spacer res
3	22	100.0	4	15	AAR56173	Sequence of cleava
4	22	100.0	4	17	AAW03712	-Gly-Phe-Leu-Gly-
5	22	100.0	4	17	AAR85710	Degradable peptide
6	22	100.0	4	18	AAW27139	Protease-sensitive
7	22	100.0	4	20	AAW99438	Interleukin-2 rece
8	22	100.0	4	20	AAW73872	Prodrug P1 peptide
9	22	100.0	4	20	AAW87722	Spacer used in the
10	22	100.0	4	21	AAY82921	Peptide exhibiting
11	22	100.0	4	22	AAE12101	Target-receptor-bi
12	22	100.0	4	22	AAU08989	Tetrapeptide linke
13	22	100.0	4	22	AAB99913	HPMA copolymer and
14	22	100.0	4	22	AAB59837	Peptide used in a
15	22	100.0	4	22	AAB60070	Peptide prodrug pe
16	22	100.0	4	22	AAY85641	Peptide used in in
17	22	100.0	4	22	AAB86849	Cathepsin-associat
18	22	100.0	4	23	ABB08358	Enzyme-degradable
19	22	100.0	5	15	AAR44699	Peptide spacer res
20	22	100.0	5	15	AAR44708	Peptide spacer res
21	22	100.0	6	14	AAR65693	Cathepsin D-inhibi
22	22	100.0	6	14	AAR37175	Aspartic proteinas
23	22	100.0	6	14	AAR37176	Aspartic proteinas
24	22	100.0	6	14	AAR37177	Aspartic proteinas
25	22	100.0	6	14	AAR37178	Aspartic proteinas
26	22	100.0	6	15	AAR44700	Peptide spacer res
27	22	100.0	6	15	AAR44714	Peptide spacer res

28	22	100.0	6	15	AAR56176	Sequence of peptid
29	22	100.0	6	18	AAW27689	Component of human
30	22	100.0	6	23	ABB78713	Amphipathic sequen
31	22	100.0	7	15	AAR44715	Peptide spacer res
32	22	100.0	8	22	ABP12025	HIV A02 super moti
33	22	100.0	8	22	ABP19916	HIV A03 motif env
34	22	100.0	8	22	ABP19991	HIV A03 motif env
35	22	100.0	8	22	ABP20155	HIV A03 motif env
36	22	100.0	8	22	ABP20303	HIV A03 motif env
37	22	100.0	8	22	AAM22467	HIV peptide SEQ ID
38	22	100.0	8	22	AAM22611	HIV peptide SEQ ID
39	22	100.0	8	22	AAM22612	HIV peptide SEQ ID
40	22	100.0	8	22	AAM22613	HIV peptide SEQ ID
41	22	100.0	8	22	AAM22630	HIV peptide SEQ ID
42	22	100.0	8	22	AAM22631	HIV peptide SEQ ID
43	22	100.0	8	22	AAM22657	HIV peptide SEQ ID
44	22	100.0	8	22	AAM22658	HIV peptide SEQ ID
45	22	100.0	8	22	AAM22659	HIV peptide SEQ ID
46	22	100.0	8	22	AAM22691	HIV peptide SEQ ID
47	22	100.0	8	22	AAM22692	HIV peptide SEQ ID
48	22	100.0	8	22	AAM23416	HIV peptide SEQ ID

ALIGNMENTS

RESULT 1
AAR26364
ID AAR26364 standard; peptide; 4 AA.
XX
AC AAR26364;
XX
DT 11-FEB-1993 (first entry)
XX
DE Cyclosporin-polymeric conjugate linker peptide.
XX
KW Polymeric conjugate; immunosuppressants; organ transplantation;
KW autoimmune disease.
XX
OS Synthetic.
XX
PN WO9213569-A.
XX
PD 20-AUG-1992.
XX
PF 28-JAN-1992; 92WO-C000003.

XX
PR 01-FEB-1991; 91CS-0000251.
XX
PA (GALE-) GALENA.
XX
PI Fornusek L, Jegorov A, Matha V, Rihova B, Strohalm J, Ulbrich K;
XX
DR WPI; 1992-299766/36.
XX
PT Targetted polymeric conjugate - contains cyclosporin attached via
PT methacryloylated aminoacid or peptide side chain, useful as
PT immunosuppressant and effective at low doses
XX
PS Example 1; Page 4; 14pp; English.
XX
CC The peptide is used to bind cyclosporin to a polymeric carrier to
CC form a polymeric conjugate. The peptide sequence can be degraded by
CC intracellular (lysosomal) enzymes. The polymeric conjugate is an
CC immunosuppressant which is esp. for use in organ transplantation and
CC in cases of autoimmune disease. Since it can be targetted with bound
CC antibodies, relatively small doses of cyclosporin are necessary, so
CC that the toxic side effects of free cyclosporin are avoided.
CC See also AAR26365 and AAR26366.
XX
SQ Sequence 4 AA;

Query Match 100.0%; Score 22; DB 13; Length 4;
Best Local Similarity 100.0%; Pred. No. 7.8e+05;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 1 GFLG 4

RESULT 2
AAR44693
ID AAR44693 standard; peptide; 4 AA.
XX
AC AAR44693;
XX
DT 06-DEC-1994 (first entry)
XX
DE Peptide spacer residue in paclitaxel copolymer conjugate.
XX

KW Paclitaxel; taxol; antitumour; conjugate; copolymer; water soluble;
KW low toxicity; polymethacrylamide.
XX
OS Synthetic.
XX
FH Key Location/Qualifiers
FT Modified-site 1
FT /note= "N-acylated by methacryloyl which is part
FT of a polymethacrylamide backbone"
FT Modified-site 4
FT /note= "carboxy group forms ester linkage with
FT OH at the 7- or 2'-position of paclitaxel"
XX
PN WO9400156-A.
XX
PD 06-JAN-1994.
XX
PF 07-JUN-1993; 93WO-EP01433.
XX
PR 19-JUN-1992; 92GB-0013077.
PR 07-JUN-1993; 93WO-EP01433.
XX
PA (FARM) FARMITALIA ERBA SRL CARLO.
XX
PI Angelucci F, Biasoli G, Mongelli N, Pesenti E, Suarato A;
XX
DR WPI; 1994-025897/03.
XX
PT New (meth)acrylamide copolymer bound paclitaxel derivs. - used
PT as antitumour agents with high water solubility and low toxicity
XX
PS Claim 1; Page 25; 32pp; English.
XX
CC The invention relates to new polymer conjugates consisting of 90 -
CC 99.9 mol% N-(2-hydroxypropyl) methacrylamide units, 0.1-5 mol%
CC paclitaxel-contg. N-substd. methacrylamide units, and 0-9.9 mol%
CC other (non-paclitaxel-contg.) N-substd. methacrylamide units. The
CC paclitaxel-contg. units consist of a methacrylamide backbone unit
CC linked via the group -NH-CH2-CO-A- (where the NH belongs to the
CC methacrylamide) by an ester group to the OH at the 7 or 2' position
CC of paclitaxel. The group A is a direct bond or a specified amino
CC acid or peptide spacer of up to 6 amino acids. The present sequence
CC is one of the specified spacer peptides which includes the initial
CC Gly from the methacrylamide unit. These spacer peptides may also be
CC present in the optional, non-paclitaxel-contg. N-substd. meth-

CC acrylamide units.
CC Paclitaxel is a taxol antitumour agent showing activity against
CC e.g.sarcoma, carcinoma, lymphoma, neuroblastoma, myeloma, Wilms
CC tumour, leukaemia and adenosarcoma. In the conjugated form within
CC the methacrylamide copolymer, the drug has higher water solubility
CC and lower toxicity. It is suitable for administration by i.v.
CC injection or infusion. The conjugate is broken down within the cell
CC to release the paclitaxel.
XX
SQ Sequence 4 AA;

Query Match 100.0%; Score 22; DB 15; Length 4;
Best Local Similarity 100.0%; Pred. No. 7.8e+05;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 1 GFLG 4

Search completed: December 6, 2002, 10:16:08
Job time : 117 secs

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OM protein - protein search, using sw model

Run on: December 6, 2002, 10:14:06 ; Search time 56 Seconds
(without alignments)
6.867 Million cell updates/sec

Title: US-09-758-993A-1
Perfect score: 22
Sequence: 1 GFLG 4

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 283224 seqs, 96134422 residues

Total number of hits satisfying chosen parameters: 283224

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1000 summaries

Database : PIR_73:*
1: pir1:*
2: pir2:*
3: pir3:*
4: pir4:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	22	100.0	9	2	PD0027	pev-tachykinin - p
2	22	100.0	24	2	A53591	envelope protein g
3	22	100.0	28	2	S22469	hypothetical prote
4	22	100.0	51	2	A65069	hypothetical prote
5	22	100.0	54	2	F71390	H+-transporting tw
6	22	100.0	54	2	T36552	probable serine pr
7	22	100.0	57	2	D95852	hypothetical prote
8	22	100.0	59	2	E86623	hypothetical prote
9	22	100.0	59	2	B72000	hypothetical prote
10	22	100.0	61	2	B39754	myelin basic prote
11	22	100.0	64	2	F86693	hypothetical prote
12	22	100.0	65	2	S77045	transposase ssl127
13	22	100.0	68	2	S60688	env protein - huma
14	22	100.0	68	2	S60693	env protein - huma
15	22	100.0	68	2	S60696	env protein - huma
16	22	100.0	68	2	S60705	gag protein - huma
17	22	100.0	68	2	S60707	env protein - huma
18	22	100.0	68	2	S60694	env protein - huma
19	22	100.0	68	2	S60687	env protein - huma
20	22	100.0	68	2	S60692	env protein - huma
21	22	100.0	69	2	S60690	env protein - huma
22	22	100.0	69	2	S60689	env protein - huma
23	22	100.0	69	2	S60706	env protein - huma
24	22	100.0	69	2	S60691	env protein - huma
25	22	100.0	69	2	B69355	hypothetical prote
26	22	100.0	70	2	C83831	hypothetical prote

ALIGNMENTS

RESULT 1
PD0027
pev-tachykinin - penaeid shrimp (Penaeus vannamei) (fragment)
C;Species: Penaeus vannamei
C;Date: 21-Aug-1998 #sequence_revision 21-Aug-1998 #text_change 19-May-2000
C;Accession: PD0027
R;Nieto, J.; Veelaert, D.; Derua, R.; Waelkens, E.; Cerstiaens, A.; Coast, G.; Devreese, B.; Van Beeumen, J.; Calderon, J.; De Loof, A.; Schoofs, L.
Biochem. Biophys. Res. Commun. 248, 406-411, 1998
A;Title: Identification of one tachykinin- and two kinin-related peptides in the brain of the white shrimp,Penaeus vannamei.
A;Reference number: PD0027; MUID:98342103; PMID:9675150
A;Accession: PD0027
A;Molecule type: protein
A;Residues: 1-9 <NIE>
C;Comment: This peptide belongs to myotropic neuropeptides.

Query Match 100.0%; Score 22; DB 2; Length 9;
Best Local Similarity 100.0%; Pred. No. 2.8e+05;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 4 GFLG 7

Search completed: December 6, 2002, 10:18:27
Job time : 81 secs

GenCore version 5.1.3

OM protein - protein search, using sw model

Run on: December 6, 2002, 10:14:02 ; Search time 10 Seconds
(without alignments)
16.591 Million cell updates/sec

Title: US-09-758-993A-1
Perfect score: 22
Sequence: 1 GFLG 4

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 112892 seqs, 41476328 residues

Total number of hits satisfying chosen parameters: 112892

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1000 summaries

Database : SwissProt_40:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	22	100.0	17	1	TRP2_LEUMA	P81733 leucophaea
2	22	100.0	19	1	TRP3_LEUMA	P81735 leucophaea
3	22	100.0	28	1	GUN_SCHCO	P81190 schizophyll
4	22	100.0	54	1	ATP8_BRAFL	O47427 branchiosto
5	22	100.0	54	1	ATP8_BRALA	O21003 branchiosto
6	22	100.0	60	1	YTR2_SPIAU	P22042 spirochaeta
7	22	100.0	66	1	RPB1_CAEBR	P35074 caenorhabdi
8	22	100.0	69	1	Y842_ARCFU	O29416 archaeoglob
9	22	100.0	71	1	HSTI_ECOLI	P22542 escherichia
10	22	100.0	78	1	ATP6_BACAO	P25965 bacillus al
11	22	100.0	83	1	YJ60_MYCTU	P95254 mycobacteri
12	22	100.0	96	1	PFPB_ENTHI	Q24824 entamoeba h
13	22	100.0	102	1	YD63_MYCPN	P75418 mycoplasma
14	22	100.0	103	1	ANFB_BOVIN	P13204 bos taurus
15	22	100.0	103	1	HE2_HUMAN	Q08648 homo sapien
16	22	100.0	112	1	YF88_METJA	Q58983 methanococc
17	22	100.0	114	1	YQJZ_BACSU	P54563 bacillus su
18	22	100.0	117	1	GP49_BPSP1	O48403 bacteriopha
19	22	100.0	118	1	HML2_HIRME	P21523 hirudo medi
20	22	100.0	119	1	CRCB_NEIMA	Q9jul1 neisseria m

ALIGNMENTS

RESULT 1
TRP2_LEUMA
ID TRP2_LEUMA STANDARD; PRT; 17 AA.
AC P81733; P81734;
DT 30-MAY-2000 (Rel. 39, Created)
DT 30-MAY-2000 (Rel. 39, Last sequence update)
DT 16-OCT-2001 (Rel. 40, Last annotation update)
DE Tachykinin-related peptide 2 (LemTRP 2) [Contains: Tachykinin-related
DE peptide 1 (LemTRP 1)].
OS Leucophaea maderae (Madeira cockroach).
OC Eukaryota; Metazoa; Arthropoda; Mandibulata; Pancrustacea; Hexapoda;
OC Insecta; Pterygota; Neoptera; Orthopteroidea; Dictyoptera; Blattaria;
OC Blaberoidea; Blaberidae; Leucophaea.
OX NCBI_TaxID=6988;
RN [1]
RP SEQUENCE.
RC TISSUE=Midgut;
RX MEDLINE=97053012; PubMed=8897641;
RA Muren J.E., Naessel D.R.;
RT "Isolation of five tachykinin-related peptides from the midgut of
RT the cockroach Leucophaea madera: existence of N-terminally extended
RT isoforms.";
RL Regul. Pept. 65:185-196(1996).
RN [2]
RP CHARACTERIZATION, AND MASS SPECTROMETRY.
RC TISSUE=Brain;
RX MEDLINE=97269266; PubMed=9114447;
RA Muren J.E., Naessel D.R.;
RT "Seven tachykinin-related peptides isolated from the brain of the
RT madeira cockroach; evidence for tissue-specific expression of
RT isoforms.";
RL Peptides 18:7-15(1997).
CC -!- FUNCTION: MYOACTIVE PEPTIDE. INCREASES THE AMPLITUDE AND FREQUENCY
CC OF SPONTANEOUS CONTRACTIONS AND TONUS OF HINDGUT MUSCLE.
CC -!- TISSUE SPECIFICITY: MIDGUT AND BRAIN.
CC -!- MASS SPECTROMETRY: MW=1796.4; METHOD=MALDI; RANGE=1-17.
CC -!- MASS SPECTROMETRY: MW=903.1; METHOD=MALDI; RANGE=9-17.
CC -!- SIMILARITY: SOME SIMILARITY TO TACHYKININS.
KW Tachykinin; Neuropeptide; Amidation.
FT PEPTIDE 1 17 TACHYKININ-RELATED PEPTIDE 2.
FT PEPTIDE 9 17 TACHYKININ-RELATED PEPTIDE 1.

FT MOD_RES 17 17 AMIDATION.
SQ SEQUENCE 17 AA; 1798 MW; 48577A957F4221F3 CRC64;

Query Match 100.0%; Score 22; DB 1; Length 17;
Best Local Similarity 100.0%; Pred. No. 43;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 12 GFLG 15

Search completed: December 6, 2002, 10:16:26
Job time : 35 secs

GenCore version 5.1.3

OM protein - protein search, using sw model

Run on: December 6, 2002, 10:14:02 ; Search time 30 Seconds
(without alignments)
27.473 Million cell updates/sec

Title: US-09-758-993A-1
Perfect score: 22
Sequence: 1 GFLG 4

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 671580 seqs, 206047115 residues

Total number of hits satisfying chosen parameters: 671580

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1000 summaries

Database : SPTREMBL_21:*
1: sp_archea:*
2: sp_bacteria:*

3: sp_fungi:*
4: sp_human:*
5: sp_invertebrate:*
6: sp_mammal:*
7: sp_mhc:*
8: sp_organelle:*
9: sp_phage:*
10: sp_plant:*
11: sp_rodent:*
12: sp_virus:*
13: sp_vertebrate:*
14: sp_unclassified:*
15: sp_rvirus:*
16: sp_bacteriap:*
17: sp_archeap:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	22	100.0	27	11	Q924I5	Q924i5 rattus norv
2	22	100.0	28	2	Q05574	Q05574 prochloroth
3	22	100.0	34	12	Q9E8K5	Q9e8k5 hepatitis b
4	22	100.0	40	1	O33162	O33162 methanosarc
5	22	100.0	40	16	Q8VIV8	Q8viv8 mycobacteri
6	22	100.0	48	2	Q9R5H3	Q9r5h3 escherichia
7	22	100.0	50	6	Q9MZ29	Q9mz29 pan troglod
8	22	100.0	57	16	Q92X78	Q92x78 rhizobium m
9	22	100.0	58	2	Q93NW4	Q93nw4 streptococc
10	22	100.0	58	11	P82450	P82450 rattus norv
11	22	100.0	59	15	Q03812	Q03812 human immun
12	22	100.0	59	16	Q9Z6J5	Q9z6j5 chlamydia p
13	22	100.0	59	16	Q8XN05	Q8xn05 clostridium
14	22	100.0	60	11	O09019	O09019 rattus norv
15	22	100.0	62	10	O64994	O64994 sedum obtus
16	22	100.0	62	10	O64997	O64997 quercus pal
17	22	100.0	64	12	Q81160	Q81160 hepatitis b
18	22	100.0	64	16	Q9RJ67	Q9rj67 streptomyce
19	22	100.0	64	16	Q9CI16	Q9ci16 lactococcus
20	22	100.0	65	2	Q9L658	Q9l658 enterococcu

ALIGNMENTS

RESULT 1
Q924I5
ID Q924I5 PRELIMINARY; PRT; 27 AA.
AC Q924I5;
DT 01-DEC-2001 (TrEMBLrel. 19, Created)
DT 01-DEC-2001 (TrEMBLrel. 19, Last sequence update)
DT 01-DEC-2001 (TrEMBLrel. 19, Last annotation update)
DE Glutamate receptor subunit GluR1 (Fragment).
OS Rattus norvegicus (Rat).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Rattus.
OX NCBI_TaxID=10116;
RN [1]
RP SEQUENCE FROM N.A.
RC STRAIN=WISTAR;
RX MEDLINE=21336588; PubMed=11340067;
RA Borges K., Dingledine R.;
RT "Functional organization of the GluR1 glutamate receptor promoter.";
RL J. Biol. Chem. 276:25929-25938(2001).
DR EMBL; AF302117; AAK76361.1; -.
KW Receptor.
FT NON_TER 27 27
SQ SEQUENCE 27 AA; 2952 MW; 1C9DAE1FE255F9E0 CRC64;

Query Match 100.0%; Score 22; DB 11; Length 27;
Best Local Similarity 100.0%; Pred. No. 2.7e+02;
Matches 4; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 GFLG 4
||||
Db 11 GFLG 14

Search completed: December 6, 2002, 10:17:03
Job time : 56 secs

```
=> file reg; d que l3
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STRUCTURE FILE UPDATES:    5 DEC 2002  HIGHEST RN 475231-25-5
DICTIONARY FILE UPDATES:   5 DEC 2002  HIGHEST RN 475231-25-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L1         10000 SEA FILE=REGISTRY ABB=ON  PLU=ON  GFLG/SQSP
L2           332 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL <=8
L3           218 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2


=> file caplus; d que l11
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FILE COVERS 1907 - 6 Dec 2002  VOL 137 ISS 24
FILE LAST UPDATED: 5 Dec 2002  (20021205/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.


L1         10000 SEA FILE=REGISTRY ABB=ON  PLU=ON  GFLG/SQSP
L2           332 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL <=8
```

```
L3          218 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2
L9         9732 SEA FILE=CAPLUS ABB=ON  PLU=ON  PRODRUG
L11          31 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND L9


=> d ibib ab hitrn 1-31

L15  ANSWER 1 OF 36  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:716310  CAPLUS
DOCUMENT NUMBER:          137:232920
TITLE:                    Preparation of ring system-conjugated peptides as
                          tumor targeting prodrugs activated by matrix
                          metalloproteinases
INVENTOR(S):              Mincher, David John; Turnbull, Agnes; Bibby, Michael
                          Charles; Loadman, Paul Michael
PATENT ASSIGNEE(S):       The Court of Napier University, UK; BTG International
                          Limited; Cancer Research Ventures Limited
SOURCE:                   PCT Int. Appl., 88 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2002072620      A1   20020919      WO 2002-GB1069   20020308
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                  GB 2001-5929     A  20010309
OTHER SOURCE(S):          MARPAT 137:232920
AB   Compds. A-(B)n-(Xaa)m-Y [A is a moiety comprising one of more of a
     heterocyclic, a carbocyclic, and a fused ring system which is essential
     for therapeutic activity of the compd. by action at a nucleic acid or
     protein target; B is a bivalent spacer; n is 0 or 1; Xaa is any amino acid
     residue; m is 2-100; Y is H, a cation, or a capping group] are claimed in
     which Xaa is independently selected at each repeat occurrence such as to
     form an oligopeptide or protein which is internally cleavable by a matrix
     metalloproteinase enzyme to produce a compd. of A-(B)n-(Xaa)q-Y (q is 0 or
     an integer less than m) with increased biol. activity.  Eighty-two
     anthraquinone-amino acid/peptide conjugates were prepd., including
     1-[3-(L-prolylamino)propylamino]anthraquinone trifluoroacetate (2) and
     1-[3-(D-alanyl-L-alanyl-L-alanyl-L-leucylglycyl-L-leucyl-L-
     prolylamino)propylamino]anthraquinone trifluoroacetate (8), and evaluated
     for biol. activity.  Compds. 2 and 8 showed IC50 = 4.3 and 36 .mu.M,
     resp., in vitro cytotoxicity against MAC 15A adenocarcinoma of the colon
     (exposure time 96 h).
IT   459456-17-8P 459456-25-8P
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (prepn. of anthraquinone peptide derivs. as tumor targeting
        prodrugs activated by matrix metalloproteinases)
```

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:428650 CAPLUS
DOCUMENT NUMBER: 137:15804
TITLE: Tetrapartate prodrugs, and preparation thereof
INVENTOR(S): Greenwald, Richard B.; Zhao, Hong
PATENT ASSIGNEE(S): Enzon, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002043663	A2	20020606	WO 2001-US45127	20011130
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2001031873	A1	20011018	US 2001-758993	20010112

PRIORITY APPLN. INFO.:
US 2000-728512 A 20001201
US 2001-758993 A 20010112
US 1997-992435 B2 19971217
US 1998-183557 A2 19981030

OTHER SOURCE(S): MARPAT 137:15804

AB Tetrapartate prodrug compds. I [L1 = bifunctional linker; D = leaving group, residue of compd. to be delivered into cell; Z (covalently linked to [D]n) = moiety actively transported into target cell, hydrophobic moiety, combinations thereof; Y1-Y4 = O, S, NR12; R11 = mono- or divalent polymer residue; R1, R4, R9 R10, R12 = H, C1-6 alkyl, C3-12 branched alkyl, C3-8 cycloalkyl, etc.; R2, R3, R5, R6 = H, C1-6 alkyl, C1-6 alkoxy, phenoxy, etc.; Ar (when included) forms multi-substituted arom. hydrocarbon or multi-substituted heterocyclic group; m, r, s, t, u = 0, 1; p = 0, pos. integer; n = 1, 2] are provided, together with methods of prepg. and using them. Prepn. of doxorubicin-contg. prodrugs according to the invention is described.

IT **104845-49-0D**, 2-5-Tachykinin-related peptide Ib (Cancer borealis), conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetrapartate prodrug prepn.)

L15 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:200594 CAPLUS
DOCUMENT NUMBER: 137:315886
TITLE: Influence of the structure of drug moieties on the in vitro efficacy of HPMA copolymer-geldanamycin derivative conjugates
AUTHOR(S): Kasuya, Yuji; Lu, Zheng-Rong; Kopeckova, Pavla; Tabibi, S. Esmail; Kopecek, Jindrich
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry/CCCD, University of Utah, Salt Lake City,

UT, 84112, USA
SOURCE: Pharmaceutical Research (2002), 19(2), 115-123
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose. To optimize the structure of geldanamycin (GDM) deriv. moieties attached to N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers via an enzymically degradable spacer. Methods. HPMA copolymers contg. different AR-GDM (AR = 3-aminopropyl (AP), 6-aminohexyl (AH), and 3-amino-2-hydroxypropyl AP(OH)) were synthesized and characterized. Their cytotoxicity towards the A2780 human ovarian carcinoma cells was evaluated. Results. The cytotoxic efficacy of HPMA copolymer-AR-GDM conjugates depended on the structure of AR-GDM. Particularly, HPMA copolymer-bound AH-GDM, which possessed the longest substituent at the 17-position, demonstrated the highest efficacy among the polymer-bound GDM derivs.; however the activity of free AH-GDM was lower than that of the other free AR-GDMs. The relative increase of the activity of macromol. AH-GDM when compared to AP-GDM or AP(OH)-GDM correlated with the enhanced recognition of AH-GDM terminated oligopeptide side-chains by the active site of the lysosomal enzyme, cathepsin B. Drug stability and further stabilization upon binding to HPMA copolymer also contributed to the obsd. phenomena. Conclusions. AH-GDM was found to be a suitable GDM deriv. for the design of a drug delivery system based on HPMA copolymers and enzymically-degradable spacers.

IT **471905-82-5P 471905-84-7P 471905-86-9P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(influence of structure of drug moieties on in vitro efficacy of HPMA copolymer-geldanamycin deriv. conjugates)

IT **416856-92-3P 471905-83-6P 471905-85-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(influence of structure of drug moieties on in vitro efficacy of HPMA copolymer-geldanamycin deriv. conjugates)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:184874 CAPLUS
DOCUMENT NUMBER: 136:261798
TITLE: Epitope-based vaccine compositions for inducing cellular immune responses against hepatitis B virus
INVENTOR(S): Sette, Alessandro; Sidney, John; Southwood, Scott; Vitiello, Maria A.; Livingstone, Brian D.; Celis, Esteban; Kubo, Ralph T.; Grey, Howard M.; Chesnut, Robert W.
PATENT ASSIGNEE(S): Epimmune Inc., USA
SOURCE: PCT Int. Appl., 228 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002019986	A1	20020314	WO 2000-US24802	20000908
WO 2002019986	C2	20020801		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2000078281 A5 20020322 AU 2000-78281 20000908
PRIORITY APPLN. INFO.: WO 2000-US24802 A 20000908

AB This invention uses our knowledge of the mechanisms by which antigen is recognized by T cells to develop epitope-based vaccines directed towards HBV. The epitopes are cytotoxic T lymphocyte epitopes, helper T cell epitopes, pan-DR-binding epitopes, or HLA-binding epitopes. More specifically, this application communicates our discovery of pharmaceutical compns. and methods of use in the prevention and treatment of HBV infection. The invention may also include treatment of patient-derived antigen-presenting cells such as dendritic cells with these epitopes in vitro and re-introduced back to the patient for immunotherapy of HBV infection.

IT **404946-69-6**
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; epitope-based vaccine compns. for inducing cellular immune responses against hepatitis B virus)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:112589 CAPLUS
DOCUMENT NUMBER: 136:330459
TITLE: Star Structure of Antibody-Targeted HPMA Copolymer-Bound Doxorubicin: A Novel Type of Polymeric Conjugate for Targeted Drug Delivery with Potent **Antitumor** Effect
AUTHOR(S): Kovar, Marek; Strohalm, Jiri; Etrych, Tomas; Ulbrich, Karel; Rihova, Blanka
CORPORATE SOURCE: Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, 142 20, Czech Rep.
SOURCE: Bioconjugate Chemistry (2002), 13(2), 206-215
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to compare the properties and **antitumor** potential of a novel type of antibody-targeted N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-bound doxorubicin conjugates with star structure with those of previously described classic antibody-targeted or lectin-targeted HPMA copolymer-bound doxorubicin conjugates. Classic antibody-targeted conjugates were prepd. by aminolytic reaction of the multivalent HPMA copolymer contg. side-chains ending in 4-nitrophenyl ester (ONp) reactive groups with primary NH2 groups of the antibodies. The star structure of antibody-targeted conjugates was prepd. using semitelechelic HPMA copolymer chains contg. only one reactive N-hydroxysuccinimide group at the end of the backbone chain. In both types of conjugates, B1 monoclonal antibody (mAb) was used as a targeting moiety. B1 mAb recognizes the idiotype of surface IgM on BCL1 cells. The star structure of the targeted conjugate had a narrower mol. mass distribution than the classic structure. The peak in the star structure was around 300-350 kDa, while the classic structure conjugate had a peak around 1300 kDa. Doxorubicin was bound to the HPMA copolymer

via Gly-Phe(D,L)-Leu-Gly spacer to ensure the controlled intracellular delivery. The release of doxorubicin from polymer conjugates incubated in the presence of cathepsin B was almost twice faster from the star structure of targeted conjugate than from the classic one. The star structure of the targeted conjugate showed a lower binding activity to BCL1 cells in vitro, but the cytostatic activity measured by [3H]thymidine incorporation was three times higher than that seen with the classic conjugate. Cytostatic activity of nontargeted and anti-Thy 1.2 mAb (irrelevant mAb) modified HPMA copolymer-bound doxorubicin was more than hundred times lower as compared to the star structure of B1 mAb targeted conjugate. In vivo, both types of conjugates targeted with B1 mAb bound to BCL1 cells in the spleen with approx. the same intensity. The classic structure of the targeted conjugate bound to BCL1 cells in the blood with a slightly higher intensity than the star structure. Both types of targeted conjugates had a much stronger **antitumor** effect than nontargeted HPMA copolymer-bound doxorubicin and free doxorubicin. The star structure of targeted conjugate had a remarkably higher **antitumor** effect than the classic structure: a single i.v. dose of 100 .mu.g of doxorubicin given on day 11 completely cured five out of nine exptl. animals whereas the classic structure of targeted conjugate given in the same schedule only prolonged the survival of exptl. mice to 138% of control mice. These results show that the star structure of antibody-targeted HPMA copolymer-bound doxorubicin is a suitable conjugate for targeted drug delivery with better characterization, higher cytostatic activity in vitro, and stronger **antitumor** potential in vivo than classic conjugates.

IT **213338-44-4P 228705-68-8DP**, aminolyzed, conjugates with doxorubicin and antibodies
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(star structure of antibody-targeted HPMA copolymer-bound doxorubicin for targeted **antitumor** drug delivery)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:932138 CAPLUS
DOCUMENT NUMBER: 137:226246
TITLE: Acquired and specific immunological mechanisms co-responsible for efficacy of polymer-bound drugs
AUTHOR(S): Rihova, B.; Strohalm, J.; Kubackova, K.; Jelinkova, M.; Hovorka, O.; Kovar, M.; Plocova, D.; Sirova, M.; St'astny, M.; Rozprimova, L.; Ulbrich, K.
CORPORATE SOURCE: Institute of Microbiology, Division of Immunology and Gnotobiology, Academy of Sciences of the Czech Republic, Prague, 142 20, Czech Rep.
SOURCE: Journal of Controlled Release (2002), 78(1-3), 97-114
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We present data providing new evidence that poly[N-(2-hydroxypropyl)methacrylamide] (PHPMA)-bound drugs, unlike free drugs, have both cytostatic and immunomobilizing activity (CIA). Immediately after injection, due to the high level of the drug, the main activity of the polymeric conjugate is cytotoxic and cytostatic. Later on, long-term circulating PHPMA-bound drug, at concns. lower than its minimal inhibitory levels, mobilizes the defense mechanisms of the host. Cytotoxic and cytostatic effects of drug-PHPMA were repeatedly confirmed. The following data support the concept of the immunomobilizing activity of the N-(2-hydroxypropyl)methacrylamide (HPMA) conjugates: (a) pre-treatment

with free drugs (doxorubicin, cyclosporin A) accelerates the appearance of EL4 mouse T-cell lymphoma while a similar pre-treatment with doxorubicin-PHPMA induces limited but definitive mobilization of the host's defense mechanisms; (b) mice cured of EL4 mouse T-cell lymphoma, BCL1 mouse B-cell leukemia and 38C13 mouse B-cell lymphoma by injection of doxorubicin-PHPMA conjugate targeted with monoclonal antibodies (anti-Thy 1.2 for EL4, anti-B1 for BCL1 and anti-CD71 for 38C13) and re-transplanted with a LD of the same cancer cells survive without any treatment considerably longer than control mice; (c) increased NK activity and anti-cancer antibody was detected only in animals treated with doxorubicin-PHPMA conjugate; and (d) considerably increased NK and LAK activity was seen in a human patient treated for generalized breast carcinoma with doxorubicin-PHPMA-IgG.

IT **228705-68-8**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunol. mechanisms responsible for efficacy of polymer-bound **antitumor** drugs)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:618026 CAPLUS
DOCUMENT NUMBER: 135:185444
TITLE: Conjugates targeted to target receptors
INVENTOR(S): Prakash, Ramesh K.; Anderson, Christopher G.
PATENT ASSIGNEE(S): Watson Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060848	A2	20010823	WO 2001-US5225	20010215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1255568	A2	20021113	EP 2001-912804	20010215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-507140 A2 20000218
WO 2001-US5225 W 20010215

OTHER SOURCE(S): MARPAT 135:185444

AB A conjugate for intracellular delivery of a chem. agent into a target receptor such as an interleukin-2-receptor-bearing cell, e.g., an activated T cell and cancer cell, includes a chem. agent, at least one copy of target-receptor binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand binds to a target receptor such as an IL-2 receptor on the target receptor-bearing cell and elicits endocytosis of the conjugate. The conjugate also optionally includes a biodegradable spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene

regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed. Methods of detecting a disease, such as cancer, T-cell lymphocytic leukemia, T-cell acute lymphoblastic leukemia, peripheral T-cell lymphoma, Hodgkin's disease, and non-Hodgkin's lymphoma, assocd. with elevated levels of sol. target receptor and/or IL-2 receptor also are disclosed.

IT **104845-49-0D**, 2-5-Tachykinin-related peptide Ib (Cancer borealis), conjugates
RL: BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(conjugates targeted to target receptors)

L15 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:572427 CAPLUS
DOCUMENT NUMBER: 136:330425
TITLE: Water-soluble HPMA copolymer-wortmannin conjugate retains phosphoinositide 3-kinase inhibitory activity in vitro and in vivo
AUTHOR(S): Varticovski, L.; Lu, Z.-R.; Mitchell, K.; de Aos, I.; Kopecek, J.
CORPORATE SOURCE: Department of Medicine, TUSM, St. Elizabeth's Medical Center, Boston, MA, 02135, USA
SOURCE: Journal of Controlled Release (2001), 74(1-3), 275-281
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphoinositide kinases and ATM-related genes play a central role in many physiol. processes. Activation of phosphoinositide 3-kinase (PI 3-kinase) is essential for signal transduction by many growth factors and oncogenes and may contribute to **tumor** progression. In the nanomolar range, Wortmannin (WM), a fungal metabolite, is a potent inhibitor of type I PI 3-kinase; it covalently modifies its catalytic subunit. Because WM is sol. only in org. solvents and unstable in water, there are difficulties in its use in vivo. To generate a water-sol. WM deriv., we used a conjugate of N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer and 11-O-desacetylwortmannin (DAWM), which has a slightly lower inhibitory activity than WM. We covalently attached DAWM to HPMA copolymer contg. oligopeptide (GFLG) side-chains. The final product had an estd. mol. mass of 20 kDa and contained 2 wt. % of DAWM. The HPMA copolymer (PHPMA)-DAWM conjugate inhibited type I PI 3-kinase activity in vitro and growth factor-stimulated activation of Akt in vivo; it possessed approx. 50% of the inhibitory activity of DMSO solubilized WM. The specificity and stability of the PHPMA-DAWM conjugate is currently under investigation. The new water-sol. form of WM may be useful in investigations of the role of PI 3-kinase in **tumor** progression and other cellular biol. functions in vivo.

IT **100424-72-4DP**, wortmannin conjugates
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(water-sol. methacrylamide copolymer-wortmannin conjugate retains phosphoinositide 3-kinase inhibitory activity in vitro and in vivo)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:572425 CAPLUS
DOCUMENT NUMBER: 136:330424
TITLE: Preparation and biological evaluation of polymerizable antibody Fab' fragment targeted polymeric drug delivery system
AUTHOR(S): Lu, Z.-R.; Shiah, J.-G.; Kopeckova, P.; Kopecek, J.
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry/CCCD, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Controlled Release (2001), 74(1-3), 263-268
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new polymerizable antibody Fab' fragment with a PEG spacer (MA-PEG-Fab') was prepd. from OV-TL 16 antibody, specific against the OA-3 antigen expressed on most human ovarian carcinomas. The MA-PEG-Fab' possessed a higher reactivity in the copolymn. with N-(2-hydroxypropyl)methacrylamide (HPMA) than the polymerizable Fab' fragment MA-Fab' with a short spacer. The MA-PEG-Fab' was copolymd. with HPMA and MA-Gly-Phe-Leu-Gly-Mce6 producing an Fab' targeted HPMA copolymer-Mce6 conjugate. The no. and wt. av. mol. wts. of the copolymer were 164000 and 271000 Da, resp. About two MA-PEG-Fab' fragments per chain were incorporated in the copolymer conjugates. Preliminary in vivo **antitumor** studies indicated that the Fab' targeted conjugates showed a higher efficacy of **tumor** growth inhibition in nude mice than the non-targeted conjugate.

IT **100424-71-3DP**, conjugates with mesochlorine Fab' antibody
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and biol. evaluation of polymerizable antibody Fab' fragment targeted polymeric drug delivery system)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:468203 CAPLUS
DOCUMENT NUMBER: 135:66201
TITLE: Conjugates targeted to the interleukin-2 receptor
INVENTOR(S): Prakash, Ramesh K.; Clemens, Christopher M.
PATENT ASSIGNEE(S): Watson Laboratories, Inc., USA
SOURCE: U.S., 22 pp., Cont.-in-part of U.S. Ser. No. 914,042, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6251866	B1	20010626	US 1998-128572	19980804
CA 2339085	AA	20000217	CA 1999-2339085	19990804
WO 2000007543	A2	20000217	WO 1999-US17648	19990804
WO 2000007543	A3	20000511		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,

TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9953926	A1	20000228	AU 1999-53926	19990804	
EP 1100543	A2	20010523	EP 1999-939680	19990804	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
BR 9912749	A	20010731	BR 1999-12749	19990804	
PRIORITY APPLN. INFO.:			US 1997-914042	B2	19970805
			US 1998-128572	A	19980804
			WO 1999-US17648	W	19990804

AB A compn. for intracellular delivery of a chem. agent into an interleukin-2-receptor-bearing cell, e.g. an activated T cell, includes a chem. agent and at least one copy of an interleukin-2-receptor-binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand binds to a receptor on the interleukin-2-receptor-bearing cell and elicits endocytosis of the compn. The compn. also preferably includes a spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is a polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. The compn. can further comprise a carrier such as another water sol. polymer, liposome, or particulate. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed. A method of detecting a disease, such as T-cell lymphocytic leukemia, T-cell acute lymphoblastic leukemia, peripheral T-cell lymphoma, Hodgkin's disease, or non-Hodgkin's lymphoma, assocd. with elevated levels of sol. IL-2 receptor is also disclosed.

IT **104845-49-0D**, 2-5-Tachykinin-related peptide Ib (Cancer borealis), conjugates
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(peptide conjugates targeted to the interleukin-2 receptor)

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	2001:400707 CAPLUS
DOCUMENT NUMBER:	135:189701
TITLE:	Phase I clinical and pharmacokinetic study of PNU166945, a novel water-soluble polymer-conjugated prodrug of paclitaxel
AUTHOR(S):	Terwogt, Jetske M. Meerum; Huinink, Wim W. ten Bokkel; Schellens, Jan H. M.; Schot, Margaret; Mandjes, Ingrid A. M.; Zurlo, Maria G.; Rocchetti, Marurizio; Rosing, Hilde; Koopman, Franciska J.; Beijnen, Jos H.
CORPORATE SOURCE:	The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Slotervaart Hospital, Amsterdam, 1066 CX, Neth.
SOURCE:	Anti-Cancer Drugs (2001), 12(4), 315-323 CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB I.v. administration of paclitaxel is hindered by poor water soly. of the drug. Currently, paclitaxel is dissolved in a mixt. of ethanol and Cremophor EL; however, this formulation (Taxol) is assocd. with significant side effects, which are considered to be related to the pharmaceutical vehicle. A new polymer-conjugated deriv. of paclitaxel,

PNU166945, was investigated in a dose-finding phase I study to document toxicity and pharmacokinetics. A clin. phase I study was initiated in patients with refractory solid **tumors**. PNU166945 was administered as a 1-h infusion every 3 wk at a starting dose of 80 mg/m2, as paclitaxel equiv. Pharmacokinetics of polymer-bound and released paclitaxel were detd. during the first course. Twelve patients in total were enrolled in the study. The highest dose level was 196 mg/m2, at which we did not observe any dose-limiting toxicities. Hematol. toxicity of PNU166945 was mild and dose independent. One patient developed a grade 3 neurotoxicity. A partial response was obsd. in one patient with advanced breast cancer. PNU166945 displayed a linear pharmacokinetic behavior for the bound fraction as well as for released paclitaxel. The study was discontinued prematurely due to severe neurotoxicity obsd. in addnl. rat studies. The presented phase I study with PNU166945, a water-sol. polymeric drug conjugate of paclitaxel, shows an alteration in pharmacokinetic behavior when paclitaxel is administered as a polymer-bound drug. Consequently, the safety profile may differ significantly from std. paclitaxel.

IT **154330-65-1**, PNU166945
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(phase I clin. and pharmacokinetic study of PNU166945, a novel water-sol. polymer-conjugated prodrug of paclitaxel)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:351063 CAPLUS
Correction of: 2001:265260

DOCUMENT NUMBER: 134:365695
Correction of: 134:309684

TITLE: Inducing cellular immune responses to human immunodeficiency virus-1 using peptide and nucleic acid compositions

INVENTOR(S): Sette, Alessandro; Sidney, John; Southwood, Scott; Livingston, Brian D.; Chesnut, Robert; Baker, Denise Marie; Celis, Esteban; Kubo, Ralph T.; Grey, Howard M.

PATENT ASSIGNEE(S): Epimmune Inc., USA

SOURCE: PCT Int. Appl., 448 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001024810 A1		20010412	WO 2000-US27766	20001005

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-412863 19991005

AB This invention uses knowledge of the mechanisms by which antigens are recognized by T cells to identify and prep. human immunodeficiency virus (HIV) epitopes, and to develop epitope-based vaccines directed towards HIV. More specifically, this application communicates the discovery of

pharmaceutical compns. and methods of use in the prevention and treatment of HIV infection.

IT **334725-52-9 340248-23-9 340248-63-7 340249-52-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epitopes of HIV-1, cytotoxic T lymphocyte and helper T lymphocyte as vaccine for inducing cellular immune responses to human immunodeficiency virus-1)

L15 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:309414 CAPLUS
DOCUMENT NUMBER: 135:262094
TITLE: New HPMA copolymers containing doxorubicin bound via pH-sensitive linkage: synthesis and preliminary in vitro and in vivo biological properties
AUTHOR(S): Etrych, T.; Jelinkova, M.; Rihova, B.; Ulbrich, K.
CORPORATE SOURCE: Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Prague, 162 06, Czech Rep.
SOURCE: Journal of Controlled Release (2001), 73(1), 89-102
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this paper we describe the synthesis, physico-chem. characteristics and results of tests of biol. activity of polymer drugs based on conjugates of anti-cancer drug doxorubicin (Dox) with water-sol. polymer drug carriers, N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers. In the conjugates the drug is attached to the polymer backbone via a spacer stable under physiol. conditions (pH 7.4) and hydrolytically degradable in mild acidic environment (e.g., endosomes, pH.apprx.5). This enables designing polymer drugs with long blood circulation and release and specific activation of the active compd. in endosomes of target cells. Two types of Dox conjugates differing in the length and structure of the oligopeptide spacer were synthesized (GG and GFLG). In both types, the linkage susceptible to hydrolytic cleavage was formed by the reaction of the carbonyl group of Dox with the hydrazide group terminating the oligopeptide side chains of the polymer. In vitro incubation of conjugates in buffers resulted in much faster release of Dox from the polymer at pH 5 than at pH 7.4 (more than 10 times) the rate being higher for the conjugate contg. GG spacer. The presence of cathepsin B in incubation media increased the rate of Dox release from the conjugate with GFLG spacer, Dox release from conjugate with GG spacer remained unchanged. Cytotoxicity of conjugates for T-splenocytes and mouse EL-4 T cell lymphoma cells was much higher compared with the effect of similar 'classic' conjugates bearing Dox attached via amide bond. In vivo anti-**tumor** activity of conjugates contg. hydrolytically sensitive linkage was also significantly improved in mouse EL4 T cell lymphoma.

IT **228705-68-8DP**, conjugates with doxorubicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(new HPMA copolymers contg. doxorubicin bound via pH-sensitive linkage)

IT **213338-44-4P 228705-68-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(new HPMA copolymers contg. doxorubicin bound via pH-sensitive linkage)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:265260 CAPLUS
DOCUMENT NUMBER: 134:309684
TITLE: Inducing cellular immune responses to human immunodeficiency virus-1 using peptide and nucleic acid compositions
INVENTOR(S): Sette, Alessandro; Sidney, John; Southwood, Scott; Livingston, Brian D.; Chesnut, Robert; Baker, Denise Marie; Celis, Esteban; Kubo, Ralph T.; Grey, Howard M.
PATENT ASSIGNEE(S): Epimmune Inc., USA
SOURCE: PCT Int. Appl., 448 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001024810 A1		20010412	WO 2000-US27766	20001005

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-412863 19991005
AB This invention uses knowledge of the mechanisms by which antigens are recognized by T cells to identify and prep. human immunodeficiency virus (HIV) epitopes, and to develop epitope-based vaccines directed towards HIV. More specifically, this application communicates the discovery of pharmaceutical compns. and methods of use in the prevention and treatment of HIV infection.
IT **334725-52-9**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV-1 supermotif peptide; epitopes of HIV-1, cytotoxic T lymphocyte and helper T lymphocyte as vaccine for inducing cellular immune responses to human immunodeficiency virus-1)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:880998 CAPLUS
DOCUMENT NUMBER: 134:46792
TITLE: Vitamin directed dual targeting therapy
INVENTOR(S): Russell-Jones, Gregory John; McEwan, John Fergus
PATENT ASSIGNEE(S): Biotech Australia Pty Limited, Australia
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074721	A1	20001214	WO 2000-AU618	20000531

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,

CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: AU 1999-712 A 19990602

AB The invention relates to vitamin-mediated targeting for the delivery of agents and active substances in the therapy of disease. Combined targeting using vitamins essential for cancer growth are used in complexes of the invention for the amplified delivery of cytotoxic drugs to **tumors** and cancer cells, with a concomitant redn. in toxicity to the subject being treated. Peptide polymers were prepd. and conjugated with vitamins such as folic acid or cobalamin. Chlorambucil-peptide conjugate prodrugs were also prepd.

IT **104845-49-0**, 2-5-Tachykinin-related peptide Ib (Cancer borealis)
RL: RCT (Reactant); RACT (Reactant or reagent)
(vitamin directed dual targeting therapy)

IT **104845-49-0DP**, 2-5-Tachykinin-related peptide Ib (Cancer borealis), conjugates with vitamins
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(vitamin directed dual targeting therapy)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:790281 CAPLUS
DOCUMENT NUMBER: 133:355236
TITLE: Amplification of folate-mediated targeting to **tumor** cells using polymers
INVENTOR(S): Russell-jones, Gregory John; Mcewan, John Fergus
PATENT ASSIGNEE(S): Biotech Australia Pty Limited, Australia
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066091	A1	20001109	WO 2000-AU406	20000504
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206252	A1	20020522	EP 2000-920286	20000504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: AU 1999-147 A 19990504
WO 2000-AU406 W 20000504

AB The invention relates to the delivery of drug, peptide and protein pharmaceuticals using the folate-mediated uptake system. More

particularly the invention relates to the amplification of drug/pharmaceutical delivery with the folate uptake system using a folate-polymer complex. The invention also relates to processes for prepg. the complexes, pharmaceutical compns. contg. same, methods of treatment involving the complexes and uses of the complexes in the manuf. of pharmaceuticals. An N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer was synthesized as a polymer backbone for the incorporation and derivatization with both the cytotoxic drug, daunomycin and folate. A biodegradable polymer (HPMA-GFLG) was synthesized by the free radical copolymn. of HPMA with N-methacryloylglycylphenylleucinylglycine p-nitrophenol ester. To incorporate daunomycin and folate onto the polymers, they were treated with a 10-M excess of a mixt. of aminohexyl-folate and daunomycin. Unreacted nitrophenyl esters were subjected to aminolysis by the addn. of 1-amino-2-propanol.

IT **100424-72-4DP**, reaction products with folate derivs. and **antitumor** agents **104845-49-0DP**, 2-5-Tachykinin-related peptide Ib (Cancer borealis), conjugate with methotrexate, reaction products with folate and **antitumor** agents **305344-57-4DP**, reaction products with folate and **antitumor** agents
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amplification of folate-mediated targeting to **tumor** cells using polymers)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 17 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:697813 CAPLUS
DOCUMENT NUMBER: 134:136539
TITLE: Time- and concentration-dependent apoptosis and necrosis induced by free and HPMA copolymer-bound doxorubicin in human ovarian carcinoma cells
AUTHOR(S): Demoy, M.; Minko, T.; Kopeckova, P.; Kopecek, J.
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Controlled Release (2000), 69(1), 185-196
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A2780 sensitive and A2780/AD doxorubicin (DOX) resistant human ovarian carcinoma cells were exposed to different concns. (0.25, 0.5, 1, 5 and 10.times.IC50) of free and HPMA copolymer-bound DOX for 12, 24, 36, 48, 60 and 72 h. Apoptosis and necrosis were evaluated using the FITC-conjugated annexin V and propidium iodide staining. The data obtained showed that the induction of apoptosis and necrosis by both free DOX and HPMA copolymer-bound DOX were time- and concn.-dependent. The data also showed significant differences between the drugs. It was found that: (i) under the action of HPMA copolymer-bound doxorubicin the alterations in the plasma membrane permeability preceded disturbances in cellular metab.; (ii) HPMA copolymer-bound doxorubicin kills the cells mainly by necrosis; (iii) HPMA copolymer-bound doxorubicin is a more effective anticancer drug than free doxorubicin.

IT **321855-36-1D**, conjugates with doxorubicin, aminolyzed
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(time- and concn.-dependent apoptosis and necrosis induced by free and HPMA copolymer-bound doxorubicin in human ovarian carcinoma cells)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:672178 CAPLUS
DOCUMENT NUMBER: 134:242513
TITLE: **Tumor** targeting of doxorubicin bound to PEG of different size and shape
AUTHOR(S): Veronese, F. M.; Schiavon, O.; Pasut, G.; Duncan, R.; Ford, J.; Andersson, L.; Andersen, A. J.; Ferruti, P.; Vincenzi, V.; Cassidy, J.; Davies, J. W.; Orsolini, P.; Deuschel, C.
CORPORATE SOURCE: University of Padua, Italy
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (2000), 27th, 498-499
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of size and shape on the elimination rate and body distribution of a conjugate contg. an **antitumor** drug, polyethylene glycol and peptide was demonstrated. Four different lysosomotropic peptide spacers between PEG and a drug (doxorubicin) were considered. Free doxorubicin is cleared from blood and from all the organs more rapidly than that bound to the conjugates. Liver is an organ of high accumulation but the highest accumulation takes place in **tumor** and this is dependent upon the size and wt. of the conjugate.
IT **329967-77-3D**, conjugates with doxorubicin and PEG
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**tumor** targeting of doxorubicin bound to PEG of different size and shape)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 19 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:649039 CAPLUS
DOCUMENT NUMBER: 133:317302
TITLE: Antiproliferative Effect of a Lectin- and Anti-Thy-1.2 Antibody-Targeted HPMA Copolymer-Bound Doxorubicin on Primary and Metastatic Human Colorectal Carcinoma and on Human Colorectal Carcinoma Transfected with the Mouse Thy-1.2 Gene
AUTHOR(S): Rihova, B.; Jelinkova, M.; Strohalm, J.; St'astny, M.; Hovorka, O.; Plocova, D.; Kovar, M.; Draberova, L.; Ulbrich, K.
CORPORATE SOURCE: Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, 142 20, Czech Rep.
SOURCE: Bioconjugate Chemistry (2000), 11(5), 664-673
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this study was to compare the potential of two plant lectins [peanut agglutinin (PNA) and wheat germ agglutinin (WGA)], monoclonal antibody (anti-Thy-1.2), its F(ab')2 fragments, and galactosamine as targeting moieties bound to the polymer drug carrier to deliver a xenobiotic, doxorubicin, to selected cancer cell lines. The authors have used primary (SW 480, HT 29) and metastatic (SW 620) human colorectal cancer cell lines and a transfectant, genetically engineered SW 620 cell line with mouse gene Thy-1.2 (SW 620/T) to test the possibility of marking

human cancer with xenogeneic mouse gene and use it for effective site-specific targeting. The targeting moieties and doxorubicin were conjugated to a water-sol. copolymer based on N-(2-hydroxypropyl)methacrylamide (HPMA) acting as a carrier responsible for controlled intracellular release of the targeted drug. FACS anal. showed a strong binding of WGA-FITC to all tested cell lines. Binding of PNA-FITC was considerably weaker. The in vitro antiproliferative effect of lectin-targeted HPMA carrier-bound doxorubicin evaluated as [3H]TdR incorporation reflected both the intensity of the binding and the different sensitivity of the tested cancer cells lines to doxorubicin. The antiproliferative effect of conjugates targeted with WGA was comparable to that with the conjugates targeted with the anti-Thy-1.2 monoclonal antibody or their F(ab')2 fragments. The magnitude of the cytotoxic effect of HPMA-doxorubicin targeted with PNA was lower in all tested cell lines. While the conjugates with WGA were more cytotoxic, the conjugates with PNA were more specific as their binding is limited to cancer cells and to the sites of inflammation. Noncytotoxic conjugates with a very low concn. of doxorubicin and targeted with PNA, anti-Thy-1.2, or their F(ab')2 fragments exerted in some lines (SW 480, SW 620) low mitogenic activity. The Thy-1.2 gene-transfected SW 620 metastatic colorectal cancer cell line was sensitive to the antiproliferative effect of Thy-1.2-targeted doxorubicin as was shown for the Thy-1.2+ EL4 cell line and for Thy-1.2+ Con A-stimulated mouse T lymphocytes. These results represent the first indication of the suitability of transfection of human cancer cells with selected targeting genes for site-specific therapy of malignancies.

IT **213338-45-5DP**, conjugates with doxorubicin and targeting moieties
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(antiproliferative effect of lectin- and anti-thy-1.2 antibody-targeted HPMA copolymer-bound doxorubicin on colorectal carcinoma in relation to transfection with thy-1.2 gene)

IT **213338-44-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(antiproliferative effect of lectin- and anti-thy-1.2 antibody-targeted HPMA copolymer-bound doxorubicin on colorectal carcinoma in relation to transfection with thy-1.2 gene)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 20 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:457905 CAPLUS
DOCUMENT NUMBER: 133:212980
TITLE: Synthesis of Starlike N-(2-Hydroxypropyl)methacrylamide Copolymers: Potential Drug Carriers
AUTHOR(S): Wang, Dong; Kopeckova, Pavla; Minko, Tamara; Nanayakkara, Vajira; Kopecek, Jindrich
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry/CCCD Mass Spectrometry Facility and Department of Bioengineering, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Biomacromolecules (2000), 1(3), 313-319
CODEN: BOMAF6; ISSN: 1525-7797
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Starlike HPMA copolymers were synthesized by conjugating semitelechelic

poly[N-(2-hydroxypropyl)methacrylamide] macromols. (ST-PHPMA, arm) with PAMAM dendrimers (core: G2, G3, G4). ST-PHPMA was synthesized by chain transfer free radical polymn., and the terminal -COOH was activated with N-hydroxysuccinimide. Doxorubicin (DOX) was introduced into the starlike HPMA copolymer to evaluate its potential as a drug delivery system. The polymers were characterized with SEC, NMR, and UV. Cytotoxicity of the DOX contg. starlike HPMA copolymer was detd. on an A2780 human ovarian carcinoma cell line and compared with DOX-contg. linear HPMA copolymers. The rate of in vitro DOX release from polymer-DOX conjugates in the presence of cathepsin B (CP-B, lysosomal cysteine proteinase) was detd. and correlated with cytotoxicity results.

IT **264192-22-5P 290308-66-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of starlike N-(2-hydroxypropyl)methacrylamide copolymers as potential drug carriers)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 21 OF 36 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:414377 CAPLUS
DOCUMENT NUMBER: 133:198462
TITLE: Hydrophilic polymers for drug delivery
AUTHOR(S): Ulbrich, K.; Subr, V.; Pechar, M.; Strohalm, J.; Jelinkova, M.; Rihova, B.
CORPORATE SOURCE: Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Prague, 16206/6, Czech Rep.
SOURCE: Macromolecular Symposia (2000), 152(Polymers Friendly for the Environment), 151-162
CODEN: MSYMEC; ISSN: 1022-1360
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Synthesis and results of biol. evaluation of two types of water-sol. polymer drug carrier systems designed for site-specific therapy are described. In the first system, a nondegradable poly[N-(2-hydroxypropyl)methacrylamide] (PHPMA) bears biodegradable oligopeptide side chains, terminated in the targeting antibody and/or anti-cancer drug doxorubicin, randomly distributed along the polymer chain. The other system is based on PEG (Mw 2000) blocks connected with biodegradable N2,N6-bis(glutamyl)-lysine oligopeptide links. This linear water-sol. polymer bears doxorubicin attached to the carboxylic groups of amino acid residues in the oligopeptide links via biodegradable GlyPheLeuGly spacer. Both systems release doxorubicin in vitro after incubation with lysosomal enzyme cathepsin B and exhibit in vivo anti-cancer activity in the treatment of selected model mice cancers. PHPMA, PEG and PHPMA-drug carriers, if conjugated with the antibody to form antibody-targeted systems, significantly decrease its immunogenicity (approx. by order of magnitude two).

IT **182361-05-3P 182361-07-5P 263707-68-2P**
263707-70-6P 263707-74-0DP, conjugate with Glu2Lys-linked PEG deriv. **263707-74-0P 263707-75-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(hydrophilic polymers for drug delivery)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:138911 CAPLUS
DOCUMENT NUMBER: 133:79138
TITLE: Poly[N-(2-hydroxypropyl)methacrylamide] conjugates of bovine seminal ribonuclease. Synthesis, physicochemical, and preliminary biological evaluation
AUTHOR(S): Ulbrich, Karel; Strohalm, Jiri; Plocova, Daniela; Oupicky, David; Subr, Vladimir; Soucek, Josef; Pouckova, Pavla; Matousek, Josef
CORPORATE SOURCE: Academy of Sciences of the Czech Republic, Institute of Macromolecular Chemistry, Prague, 162 06/6, Czech Rep.
SOURCE: Journal of Bioactive and Compatible Polymers (2000), 15(1), 4-26
CODEN: JBCPEV; ISSN: 0883-9115
PUBLISHER: Technomic Publishing Co., Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis of three conjugates of poly(HPMA) with bovine seminal RNase (BS-RNase) differing in their structure is described. Two conjugates contained BS-RNase conjugated with the polymer via functional group situated at the end of the polymer chain (star-shaped conjugate I) or attached to the poly(HPMA) carrier via biodegradable oligopeptide spacers randomly distributed along the polymer chain ("classic" conjugate II). These two conjugates differ in structure, mol. wt., and mol. wt. distribution. In addn., a conjugate combining the activity of two compds., BS-RNase and doxorubicin, both attached to the same polymer chain via biodegradable spacers was synthesized ("classic" conjugate III). Biol. activity of all BS-RNase conjugates was compared with that of free BS-RNase and to the polymer-bound anticancer drug doxorubicin (conjugate IV). Unlike the bovine pancreatic RNase (RNase A), BS-RNase displays a potent **antitumor** activity when tested in vitro and, if administered intratumorally, also in vivo. BS-RNase in its polymer-conjugated forms (conjugates I, II and III) tested on various human **tumor** cell lines has lost at least part of its **antitumor** activity. In in vivo expts. (nude mice bearing human melanoma), intratumoral (i.t.) therapy with BS-RNase or with its conjugates II and III showed a significant **antitumor** effect. I.v. (i.v.) application of free BS-RNase was totally ineffective, while both BS-RNase conjugates II and III caused significant inhibition of **tumor** growth. BS-RNase bound to a star-shaped polymer (conjugate I) and administered i.t. or i.v. at the same concn. showed very high toxicity. Our results demonstrate that modification of BS-RNase with poly(HPMA) can prevent it from degrading or inactivating events occurring in blood vessels after i.v. application, significantly enhancing its potential for therapeutical application.

IT **228705-68-8DP**, aminolyzed, conjugates with doxorubicin and RNase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and **antitumor** activity of poly(hydroxypropyl)methacrylamide conjugates of bovine seminal RNase)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 23 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:116860 CAPLUS
DOCUMENT NUMBER: 132:171073
TITLE: Conjugates targeted to target receptors and/or interleukin-2 receptors
INVENTOR(S): Prakash, Ramesh K.; Clemens, Christopher M.

PATENT ASSIGNEE(S): Watson Laboratories, Inc.-Utah, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000007543	A2	20000217	WO 1999-US17648	19990804
WO 2000007543	A3	20000511		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6251866	B1	20010626	US 1998-128572	19980804
CA 2339085	AA	20000217	CA 1999-2339085	19990804
AU 9953926	A1	20000228	AU 1999-53926	19990804
EP 1100543	A2	20010523	EP 1999-939680	19990804
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9912749	A	20010731	BR 1999-12749	19990804

PRIORITY APPLN. INFO.:
US 1998-128572 A 19980804
US 1997-914042 B2 19970805
WO 1999-US17648 W 19990804

AB A compn. for intracellular delivery of a chem. agent into a target receptor and/or interleukin-2-receptor-bearing cell, e.g. an activated T cell and cancer cell, includes a chem. agent, at least one copy of target-receptor binding and/or an interleukin-2-receptor-binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand binds to a target receptor and/or IL-2 receptor on the target receptor and/or IL-2-receptor-bearing cell and elicits endocytosis of the compn. The compn. also optionally includes a biodegradable spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. The compn. can further comprise a carrier such as another water sol. polymer, liposome, or particulate. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed. A method of detecting a disease, such as cancer, T-cell lymphocytic leukemia, T-cell acute lymphoblastic leukemia, peripheral T-cell lymphoma, Hodgkin's disease, and non-Hodgkin's lymphoma, assocd. with elevated levels of sol. target receptor and/or IL-2 receptor is also disclosed.

IT **104845-49-0D**, 2-5-Tachykinin-related peptide Ib (Cancer borealis), conjugates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(conjugates targeted to target receptors and/or interleukin-2 receptors)

L15 ANSWER 24 OF 36 CAPLUS

ACCESSION NUMBER: 2000:46561 CAPLUS
DOCUMENT NUMBER: 132:298650
TITLE: Polymeric drugs based on conjugates of synthetic and natural macromolecules I. Synthesis and physico-chemical characterization
AUTHOR(S): Ulbrich, K.; Subr, V.; Strohalm, J.; Plocova, D.; Jelinkova, M.; Rihova, B.
CORPORATE SOURCE: Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Prague, 162 06, Czech Rep.
SOURCE: Journal of Controlled Release (2000), 64(1-3), 63-79
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This paper describes the synthesis, physico-chem. characteristics and results of selected biol. tests of conjugates of antibodies or proteins with poly(HPMA) or with poly(HPMA) carriers of anti-cancer drug doxorubicin, designed for targeted cancer therapy. Two types of conjugates differing in the method of conjugation of polymer with protein were synthesized. In the first, protein is attached to the polymer via an oligopeptide sequence in the side chain of the polymer backbone and, in the second, the polymer is attached to protein via its end-chain functional group. Conjugation of an antibody with poly(HPMA) does not influence the binding activity of the antibody for cell surface antigen. The physico-chem. characteristics and biol. activity of both systems depend on the detailed structure of the polymer, the type of antibody or protein moiety and the structure of the whole system.

IT **100424-72-4P 213338-44-4DP**, conjugates with antibodies **228705-68-8P 264192-20-3P 264192-22-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HPMA-peptide copolymer conjugates with antibodies and **antitumor** agents)

IT **100424-71-3D**, conjugates with antibodies **264192-19-0D**, conjugates with antibodies
RL: RCT (Reactant); RACT (Reactant or reagent)
(HPMA-peptide copolymer conjugates with antibodies and **antitumor** agents)

IT **100424-71-3P 213338-44-4P 264192-19-0P 264192-21-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(HPMA-peptide copolymer conjugates with antibodies and **antitumor** agents)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:720562 CAPLUS
DOCUMENT NUMBER: 132:54713
TITLE: Polymerizable Fab' antibody fragments for targeting of anticancer drugs
AUTHOR(S): Lu, Zheng-Rong; Kopeckova, Pavla; Kopecek, Jindrich
CORPORATE SOURCE: Departments of Pharmaceutics and Pharmaceutical Chemistry/CCCD, and of Bioengineering, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Nature Biotechnology (1999), 17(11), 1101-1104
CODEN: NABIF9; ISSN: 1087-0156
PUBLISHER: Nature America

DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have designed a new pathway for the synthesis of targeted polymeric drug delivery systems, using polymerizable antibody Fab' fragments (MA-Fab'). The targeted systems can be directly prepd. by copolymn. of the MA-Fab', N-(2-hydroxypropyl)methacrylamide (HPMA) and drug-contg. monomers. Both MA-Fab' and the Fab'-targeted copolymers can effectively bind to target cells. An MA-Fab' (from OV-TL 16 Ab) targeted HPMA copolymer contg. mesochlorin e6 (Mce6) was synthesized by copolymn. of MA-Fab', HPMA, and MA-GFLG-Mce6. The targeted copolymer exhibited a higher cytotoxicity toward OVCAR-3 human ovarian carcinoma cells than the nontargeted Mce6-contg. copolymer or free Mce6. The targeted copolymer was internalized more efficiently by OVCAR-3 cells than the nontargeted copolymer.
IT **252882-13-6DP**, copolymers with polymerizable antibody fragment and methacrylamide monomer
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polymeric drug carrier contg. Fab' antibody fragments for targeting of anticancer drugs)
IT **100424-72-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of polymeric drug carrier contg. Fab' antibody fragments for targeting of anticancer drugs)
IT **252882-13-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of polymeric drug carrier contg. Fab' antibody fragments for targeting of anticancer drugs)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:245916 CAPLUS
DOCUMENT NUMBER: 131:120689
TITLE: A possibility to overcome P-glycoprotein (PGP)-mediated multidrug resistance by antibody-targeted drugs conjugated to N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer carrier
AUTHOR(S): St'astny, M.; Strohalm, J.; Plocova, D.; Ulbrich, K.; Rihova, B.
CORPORATE SOURCE: Department of Immunology and Gnotobiology, Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, 14220/4, Czech Rep.
SOURCE: European Journal of Cancer (1999), 35(3), 459-466
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers contg. doxorubicin (DOX) and different targeting moieties were developed with the aim of specific chemotherapy. Two of them, HPMA-conjugated DOX and galactosamine-targeted DOX, are in phase II clin. trials in the U.K. Here, the effects of conjugates with different targeting moieties (anti-CD71, antithymocyte globulin, anti-CD4, transferrin) on human or mouse multidrug resistance (MDR) cell lines (CEM/VLB, P388-MDR) were studied. It was shown that targeting decreases the level of MDR for DOX and the level of MDR depends on the targeting moiety used. The combination of these conjugates with chemosensitizers (cyclosporin A, D,

Ġ) restored almost completely the sensitivity of MDR cell lines to that of parental sublines. These results suggest that different intracellular trafficking of these conjugates (in membrane-limited organelles) in contrast to free diffusion for low mol. wt. compds. might partially overcome P-glycoprotein (Pgp)-mediated MDR. We also report here the development of biodegradable HPMA hydrogels suitable for prolonged release of the cytostatic drug and chemosensitizer as a potential approach to overcome MDR mediated by Pgp.

IT **100424-71-3D**, conjugates with antibodies or transferrins, doxorubicin and polymer
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibody-targeted doxorubicin conjugates with polymer carrier for overcoming P-glycoprotein-mediated multidrug resistance in **tumor** cells)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:133618 CAPLUS
DOCUMENT NUMBER: 130:187175
TITLE: Conjugates targeted to the interleukin-2 receptor
INVENTOR(S): Prakash, Ramesh K.
PATENT ASSIGNEE(S): Theratech, Inc., USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907324	A2	19990218	WO 1998-US16290	19980805
WO 9907324	A3	19990415		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1011705	A2	20000628	EP 1998-939226	19980805
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ZA 9807181	A	19990323	ZA 1998-7181	19980811

PRIORITY APPLN. INFO.: US 1997-914042 A 19970805
WO 1998-US16290 W 19980805

AB A compn. for intracellular delivery of a chem. agent into an interleukin-2-receptor-bearing cell, e.g. an activated T cell, includes a chem. agent and at least two copies of an interleukin-2-receptor-binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand binds to a receptor on the interleukin-2-receptor-bearing cell and elicits endocytosis of the compn. The compn. also optionally includes a spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. The compn. can further

comprise a carrier such as another water sol. polymer, liposome, or particulate. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed.

IT **220680-37-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates targeted to the interleukin-2 receptor)

IT **104845-49-0P**, 2-5-Tachykinin-related peptide Ib (Cancer borealis)
RL: PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(conjugates targeted to the interleukin-2 receptor)

L15 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:629682 CAPLUS
DOCUMENT NUMBER: 130:75818
TITLE: Design of lysosomotropic macromolecular prodrug of doxorubicin using N-acetyl-.alpha.-1,4-polygalactosamine as a targeting carrier to hepatoma tissue
AUTHOR(S): Ouchi, Tatsuro; Tada, Masahiro; Matsumoto, Mitsuo; Ohya, Yuichi; Hasegawa, Kaname; Arai, Yuichi; Kadowaki, Kiyoshi; Akao, Santaro; Matsumoto, Tatsuji; Suzuki, Shigeo; Suzuki, Masuko
CORPORATE SOURCE: Department of Applied Chemistry Faculty of Engineering & High Technology, Kansai University, Osaka, 564-8680, Japan
SOURCE: Journal of Bioactive and Compatible Polymers (1998), 13(4), 257-269
CODEN: JBCPEV; ISSN: 0883-9115
PUBLISHER: Technomic Publishing Co., Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .alpha.-1,4-Polygalactosamine (PGA) and N-acetylated .alpha.-1,4-polygalactosamine (NAPGA) are chitosan- and chitin-like biodegradable .alpha.-1,4-linked polysaccharides, resp. Radioactivity of 14C-50% N-acetylated PGA injected into hepatomized mice, was found to accumulate more in the liver, kidney, ileum and hepatoma **tumor** tissues, compared with other organs. To provide a lysosomotropic macromol. prodrug of doxorubicin (DXR) targeted to hepatoma **tumor** tissue, DXR was immobilized on water-sol. 6-O-carboxymethyl(CM)-NAPGA by Gly-Phe-Leu-Gly spacer groups (CM-NAPGA/Gly-Phe-Leu-Gly/DXR conjugate). The conjugate showed cathepsin B susceptible DXR release behavior and exhibited remarkable survival effects in mice bearing MH134Y hepatoma implanted by s.c. (s.c.) implantation/i.v. (i.v.) injection, compared with free DXR and CM-NAPGA-immobilized DXRs with pentamethylene spacer groups (CM-NAPGA/C5/DXR conjugate).

IT **161261-00-3DP**, conjugate with carboxymethylated N-acetyl galactosamine polymer
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(doxorubicin prodrug using N-acetyl-.alpha.-1,4-polygalactosamine as a targeting carrier to hepatoma tissue)

IT **160036-45-3P 161261-00-3P 218926-30-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(doxorubicin prodrug using N-acetyl-.alpha.-1,4-polygalactosamine as a targeting carrier to hepatoma tissue)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:592493 CAPLUS
DOCUMENT NUMBER: 129:306425
TITLE: Dilute-solution properties of a polymeric **antitumor** drug carrier by size-exclusion chromatography, viscometry, and light scattering
AUTHOR(S): Mendichi, R.; Rizzo, V.; Gigli, M.; Schieroni, A. Giacometti
CORPORATE SOURCE: Istituto di Chimica delle Macromolecole (CNR), Milan, 20133, Italy
SOURCE: Journal of Applied Polymer Science (1998), 70(2), 329-338
CODEN: JAPNAB; ISSN: 0021-8995
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An investigation is reported on the dil.-soln. properties of PNU166945, a conjugate between a synthetic polymeric drug carrier poly[N-(2-hydroxypropyl)methacrylamide] (PHPMA) and the **antitumor** drug Paclitaxel. Thirteen fractions of the conjugate PNU and six fractions of the polymeric drug-carrier PHPMA were prepd. and characterized by size-exclusion chromatog., viscometry, and light scattering. The molar mass distribution, intrinsic viscosity [.eta.], and dimensions (s2)1/2 of each fraction were detd. From M, [.eta.], and (s2)1/2, the consts. of the power laws [.eta.] = f(M) and (s2)1/2 = f(M) were detd. A Stockmayer-Fixman plot was utilized to derive the unperturbed dimensions of the macromols. The presence of the drug considerably influences the conformation of the macromols. For PHPMA and PNU, resp., the slopes of the power law [.eta.] = f(M) were 0.69 and 0.617, the slopes of the power law (s2)1/2 = f(M) were 0.55 and 0.48, and the Kuhn statistical segments were 1.7 and 2.1 nm. To our knowledge, this is the first time that an exhaustive mol. characterization of a conjugated polymeric system has been presented.
IT **154330-65-1**, PNU166945
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dil.-soln. properties of a polymeric **antitumor** drug carrier by size-exclusion chromatog., viscometry, and light scattering)

L15 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:451196 CAPLUS
DOCUMENT NUMBER: 129:183939
TITLE: Design of macromolecular prodrug of 5-fluorouracil using N-acetylpolygalactosamine as a targeting carrier to hepatoma
AUTHOR(S): Ouchi, Tatsuro; Tada, Masahiro; Matsumoto, Mitsuo; Ohya, Yuichi; Hasegawa, Kaname; Arai, Yuichi; Kadowaki, Kiyoshi; Akao, Santaro; Matsumoto, Tatsuji; Suzuki, Shigeo; Suzuki, Masuko
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, and High Technology Research Center, Kansai University, Suita, 564-8680, Japan
SOURCE: Reactive & Functional Polymers (1998), 37(1-3), 235-244
CODEN: RFPOF6; ISSN: 1381-5148
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .alpha.A-1,4-Polygalactosamine (PGA) purified from the culture fluid of Paecilomyces sp. I-1I strain and N-acetylated .alpha.-1,4-polygalactosamine (NAPGA) are chitosan- and chitin-like biodegradable, compatible .alpha.-1,4-linked polysaccharides, resp. Partially N-acetylated PGA was found to show the stronger binding activity onto MH134Y hepatoma cells than three kinds of normal lymphocytes, bone marrow, T and B cells from the results of binding assay of 14C-50% N-acetylated PGA in vitro. Since PGA and NAPGA have the unreducing end groups of galactosamine and N-acetyl galactosamine, resp., they were suggested to exhibit the receptor-mediated affinities to hepatoma cells. In order to provide the lysosomotropic macromol. prodrug of fluorouracil (5FU) having a targeting ability to hepatoma, we synthesized water-sol. 6-O-carboxymethyl-NAPGA-immobilized 5FUs through Gly-Phe-Leu-Gly, monomethylene spacer groups. The obtained conjugate showed the cathepsin-B-susceptible release behavior of 5FU and then exhibited the stronger cytotoxic activity than free 5FU against HLE hepatoma cells in vitro.

IT **192055-73-5P 200427-89-0P 211688-89-0P**
211688-91-4P 211688-93-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design of macromol. prodrug of 5-fluorouracil using N-acetylpolygalactosamine as a targeting carrier to hepatoma)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:60818 CAPLUS
DOCUMENT NUMBER: 128:145249
TITLE: HPMA-based biodegradable hydrogels containing different forms of doxorubicin: **antitumor** effects and biocompatibility
AUTHOR(S): Rihova, Blanka; Srogl, Jan; Jelinkova, Marketa; Hovorka, O.; Buresova, Magda; Subr, Vladimir; Ulbrich, Karel
CORPORATE SOURCE: Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, 14220/4, Czech Rep.
SOURCE: Annals of the New York Academy of Sciences (1997), 831(Bioartificial Organs), 57-71
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HPMA (N-2-hydroxypropylmethacrylamide)-based biodegradable hydrogels for the controlled delivery of anticancer drugs proved their in vivo **antitumor** efficacy. They showed better in vivo **antitumor** activity than the sol forms of the drug. Their in vivo **antitumor** activity is dependent on their degrdn. rate. **Antitumor** activity of the hydrogels also directly correlateds with drug (doxorubicin) content. Use of doxorubicin in the form of HPMA-based hydrogels allows a several-fold increase of the administered dose, and the hydrogel matrix itself has no toxic effects on bone marrow.

IT **100424-71-3DP**, reaction products with hydroxypropylmethacrylamide and doxorubicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**antitumor** effects and biocompatibility of hydroxypropylmethacrylamide-based biodegradable hydrogels contg. doxorubicin)

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